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Chapter 10

Proliferative Endometrial Lesions Hidden behind the Feline Pyometra

Maria dos Anjos Pires, Hugo Vilhena, Sónia Miranda, Miguel Tavares Pereira, Fernanda Seixas and Ana Laura Saraiva

Additional information is available at the end of the chapter

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Abstract

The literature refers to pyometra as the most important pathology in the feline uterus, which is often associated with cystic endometrial disease (cystic endometrial hyperplasia/pyometra complex or CEH-Pyo). The etiology of pyometra is complex and probably multifactorial, but hormonal influences are suggested to play an important role in the pathogenesis. Progestagen-based contraceptives may be risk factors for the CEH-Pyo syndrome, for endometrial adenocarcinoma and also to mammary tumors in this species.

The histopathological descriptions of pyometra include an enlarged uterus containing purulent fluid, variable endometrial infiltration of neutrophils and bacterial colonization. The degree of hyperplasia of endometrial glands is variable, and frequently the endometrium becomes atrophic. The severity of endometritis is variable. Thereby, the type of inflammatory cells infiltrating the uterine wall or lumen varies accordingly and may include neutrophils, macrophages, plasma cells and lymphocytes.

The clinical diagnosis of pyometra is often based on the clinical signs and the physical examination, supported by ultrasound findings. The surgical excision of the uterus is the recommended treatment when the animal is not intent for breeding, as most pyometra clinical signs resolve after ovariohysterectomy.

Nevertheless, our clinical practice demonstrated that, in cats, pyometra often masks other uterine conditions that may present a worst prognosis and may interfere with the expected outcome. Thus, although seldom requested, the pathological analysis of the uterus with pyometra should be performed following surgery, even if significant macroscopic alterations are not visible, as one frequent finding in pyometra specimens is the co-existence of feline endometrial adenocarcinoma (FEA).

FEA is usually described as a rare pathology in cats, but recent descriptions suggest that it may be more frequent than thought. Some morphological and clinical features of FEA, as well as molecular markers, have been recently described. Moreover, age is not an adequate factor for triage, since some FEA cases were described in young animals, prompting pathologists, clinicians and researchers into this new reality.

Therefore, this chapter proposes to highlight aspects that reinforce the need for careful observation of all the cases of CEH-Pyo, to exclude the co-existence of FEA that can worsen the prognosis.

Keywords: Cat, cystic hyperplasia, endometrial adenocarcinoma, pyometra, queen

1. Introduction

The cystic endometrial hyperplasia-pyometra (CEH-Pyo) complex is the most frequent and important uterine disorder in queens [1–5]. Ovarian hormones are considered the main factors in CEH-Pyo complex development, and progesterone is considered the principal component in its pathogenesis. Nevertheless, estrogen's effects in uterus have also been implicated as causing hyperplasia of the endometrium and cystic dilation of endometrial glands, with concomitant increased secretion of fluid that favors the progression of CEH to pyometra [6, 7]. Pyometra is characterized by uterine inflammation and infiltration of the endometrium and uterine lumen by neutrophils and bacteria, leading to the development of the clinical signs [8]. Ultimately, the condition may originate sepsis [2, 9, 10].

In queens, pyometra has been described co-existing with other uterine conditions, such as a disorder of sexual development [11], uterine torsion [12], in ovariectomized (but not hysterectomized) cats [13] and in the uterine stump of neutered queens with ovarian remnant syndrome [14, 15]. Moreover, several cases of uterine neoplasia associated with pyometra have been reported in queens [16–18]. The factors involved in the development of feline endometrial adenocarcinomas (FEA) are still unclear. However, it seems probable that the endogenous or exogenous ovarian steroid hormones that are associated with CEH and pyometra development might also influence endometrial carcinogenesis and tumor progression [1, 2, 12, 17, 18]. Moreover, one could also hypothesize that the feline uterus reacts to any irritative stimulus by enhancing the inflammatory response, like it happens in dogs, which would lead to pyometra [8].

2. Pathophysiology of the cystic endometrial hyperplasia-pyometra complex

Female cats are a polyestrous seasonal species (Figure 1). The photoperiod is a major factor influencing the onset and duration of seasonal ovarian activity [19]. During the breeding season, queens may show ovulatory or anovulatory estrous cycles. In cats, spontaneous ovulation seldom occurs. Cats are considered a species with induced ovulation in which a physical repetitive stimulus, as the one associated with coitus or mechanical stimulation of the vagina, is required to trigger a consistent pulse of pre-ovulatory luteinizing hormone (LH). This will stimulate the ovulation of large ovarian follicles, which occurs in approximately 30

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to 50 hours after the LH surge [6]. However, less frequently, ovulation can also occur without mating and is designated as spontaneous ovulation. Frequent grooming, self-grooming and presence of a tomcat are putative pheromonal, tactile and visual stimuli that may trigger LH secretion and induce ovulation [20–22].

In anovulatory cycles, recurrent follicular (estrogen-dominated) phases develop and in absence of a luteal phase, they are separated only by a short period corresponding to follicular atresia and emergence of a new follicular wave. Consequently, in non-ovulatory cycles, the uterus is not exposed to progesterone [6, 19, 22].

In ovulatory cycles, follicular and luteal (progesterone-dominated) phases alternate. The follicular stage is similar to that of non-ovulatory cycles. After ovulation, progesterone secretion by corpora lutea initiates within 24 to 48 hours. The luteal phase lasts approximately 30 days in non-pregnant cycles (diestrous or luteal phase), but it may also last up to 50 days if a pseudopregnancy develops, and in pregnant cycles the progesterone dominancy lasts about 60 days [6, 19, 22].

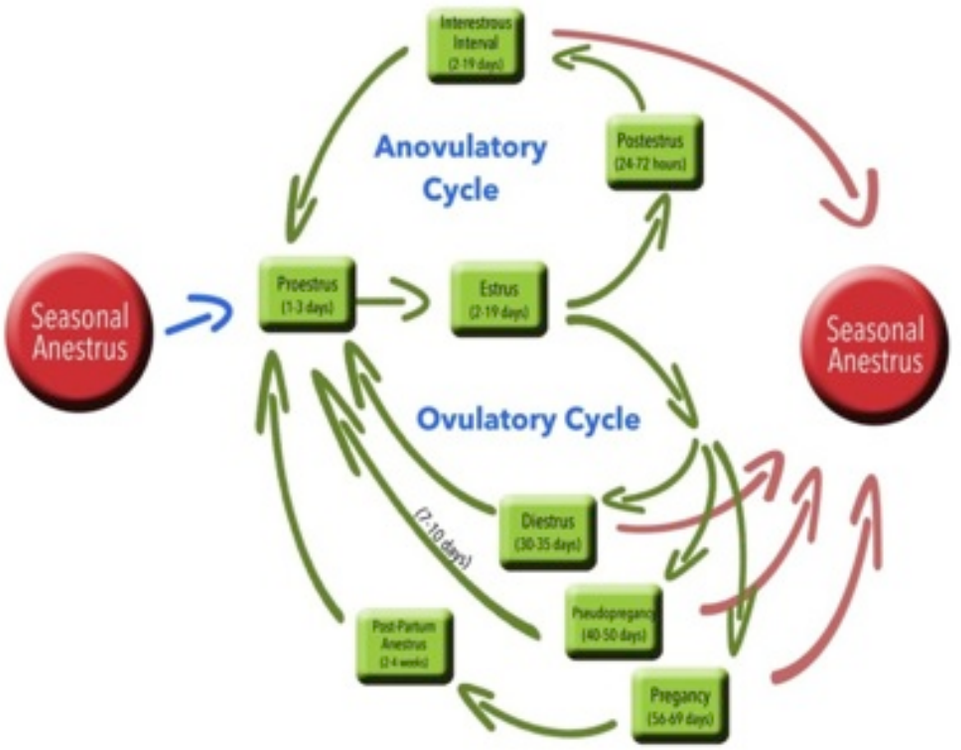

Figure 1. Drawing of the queen's reproductive cycle—the estrous cycles begin at puberty or after a seasonal anestrous. The figure compares the alternacy of the stages of the cycle in the anovulatory (top) or ovulatory (bottom) estrous cycles. The season onset always originates a new cycle whereas, at the end of season, the female can enter anestrous issued from an anovulatory cycle or at the end of a luteal phase (diestrous, pseudopregnancy or pregnancy) if the cycle was ovulatory.

The effects of progesterone in the uterus are major players in the pathogenesis of the CEH-Pyo complex. Progesterone plays diverse physiological roles designed to facilitate embryo survival

and the success of a term pregnancy. These include the following: (1) the increase in coiling and in the secretory activity of endometrial glands (which expand the surface and the amount of fluid produced), (2) the decreased myometrial contractility, (3) the closure of the uterine cervix and (4) a depression in the uterine immune response [6, 21]. Our studies showed that T lymphocytes are the most common immune cells found in the cyclic feline endometrium, and we noted a variation of these cells and macrophage localization in the uterus between follicular and luteal stages, with an apparent migration of these cell populations from the surface layers to deeper layers of the endometrium during the luteal stages, which favor the embryo implantation [23].

Repeated exposure to consecutive progesterone cycles or the exogenous administration of progestagens for contraception may aggravate these effects, and stimulate the proliferation and cystic dilation of the endometrial glands leading to CEH development, luminal fluid accumulation, and uterine distention [24]. These changes in the uterine microenvironment, in particular the accumulation of a mucinous fluid in the uterus and the immune suppression, predispose to colonization of the uterine content by ascending bacteria from vaginal microbiota, originating pyometra [2, 6, 8, 21].

Pyometra is often diagnosed with functional ovarian corpora lutea. The progesterone is considered the main hormone implicated, although estrogens are also considered important in the CEH-Pyo complex pathogenesis. The disease has also been reported in cats with ovaries containing only follicles and basal serum progesterone concentrations or in cats with inactive ovaries [5, 25]. Estrogens cause dilation of the cervix during estrous, predisposing the uterus to ascending bacterial colonization by the normal vaginal biota [2, 19, 26]. In fact, the existence of a subclinical chronic low-grade bacterial uterine infection that may develop during the proestrous or estrous has also been implicated as a causative factor responsible for the endometrial proliferation occurring earlier in the pathogenesis of the CEH-Pyo complex [8]. Moreover, estradiol increases the estrogen and progesterone receptors in the uterus and enhances uterine response to continued stimulation with estradiol and concurrent or subsequent stimulation by progesterone [21].

It is questionable who comes first in the pyometra pathology: the colonization by bacteria that promotes inflammation or the instability or anomalous morphology/physiology of the endometrium (as CEH or FEA), which endorse the proliferation of opportunist bacteria that arrive from the cervix and vagina [6]. The most common bacteria isolated from feline pyometra is *Escherichia coli*, but other agents of the normal vaginal flora and of suspected fecal contamination have been also detected, including *Streptococcus* spp., *Staphylococcus* spp., *Pasteurella* spp., *Klebsiella* spp., *Proteus* spp., *Pseudomonas* spp., *Moraxella* spp., and *Tritrichomonas foetus* [6, 19, 25, 27, 28]. Sterile pyometra may also be observed [2].

3. Epidemiology

Cystic endometrial hyperplasia/pyometra complex is considered to be frequent in female cats. However, information on prevalence of feline pyometra is scarce. The few published studies

suggest that it is less frequent than in dogs [3], which is in accordance with our experience (unpublished data). This difference has been attributed to two main factors. The first is related to the fact that queens are induced ovulators, and therefore, the feline uterus is less frequently exposed to progesterone influence [20, 24]. The second is related with the habit to neuter queens at younger ages to prevent unwanted pregnancies and heat behavior [15].

The prevalence of feline CEH-Pyo complex increases with age and is considered a common condition in cats older than 5 years of age and in cats receiving exogenous progestogens [1, 3, 5, 29–32]. Age effects in CEH-Pyo complex are associated to a cumulative effect of repeated hormonal stimulation in subsequent estrous cycles. Spontaneous ovulations and progestogen treatments predispose the uterus to abnormal endometrial proliferation, which leads to CEH development [25]. However, pyometra can also develop in younger animals, presumably due to other etiological process not yet described in the literature.

Feline breeds like the Sphynx, Siberian cat, Ocicat, Korat, Siamese, Ragdoll, Maine Coon, and Bengal seem to present a higher rate of pyometra, according to a study performed in Sweden [3]. Age at first mating, age at first parturition, and the number of parturitions do not appear to influence pyometra development [6].

Although feline pyometra is associated with a high morbidity, the mortality rate is relatively low, ranging from 5.7 to 8.0% of cases [3, 4].

4. Diagnosis

CEH is usually a silent pathology, with infertility being the main symptom in the early stages of the disease [6, 21, 33]. At this stage, queens are usually asymptomatic, and the physical examination, results from hematology, serum biochemistry, and urinalysis are unremarkable in most cases [5]. In cases of marked hyperplasia, or when mucometra develops, abdominal distention can be observed and an enlarged uterus can be detected on abdominal palpation [6]. In some cases, the uterus can be visualized on abdominal radiographs, but this diagnostic procedure presents low sensitivity in CEH. Abdominal ultrasound and histopathology are the most reliable methods for CEH diagnosis [19].

Pyometra is commonly associated with overt clinical symptoms and the abnormalities detected on complementary diagnostic exams vary with the severity of the disease, which typically develop one week to two months after estrous [2, 34]. The most common clinical symptoms include a mucous-purulent to hemorrhagic vulvar discharge (Figure 2), anorexia, lethargy, abdominal distention, dehydration, a palpable uterus, fever, and leukocytosis [4, 19]. The vulvar discharge is present in cases of open-cervix pyometra, but it can be unapparent due to the fastidious grooming habits of queens [6]. Queens with closed-cervix pyometra often have a significant abdominal distention and signs of severe illness [19].

Diagnosis is based on the history and clinical signs, and it is usually confirmed by abdominal radiography and/or ultrasound [13]. On abdominal radiology, an enlarged uterus with dorsal and cranial displacement of the small intestine can be detected, but these are also found in

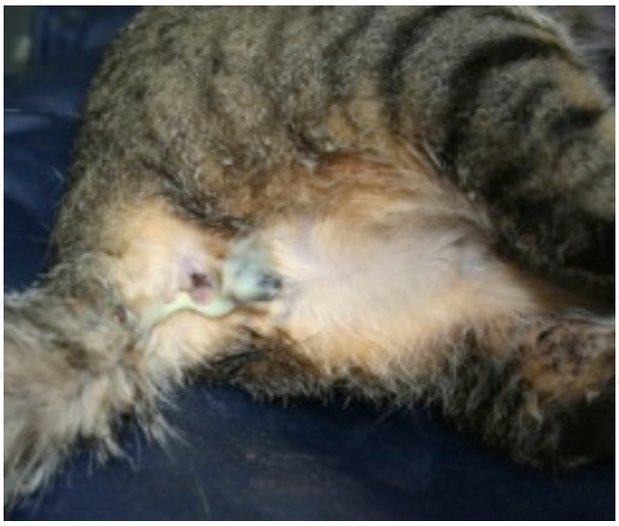

Figure 2. Purulent vulvar discharge in a queen with open-cervix pyometra.

early pregnancy [6]. In the abdominal ultrasound, it is possible to observe an enlarged uterus containing hypoechoic to anechoic intraluminal fluid (Figures 3A and B). This is the diagnostic procedure of choice in most cases [25].

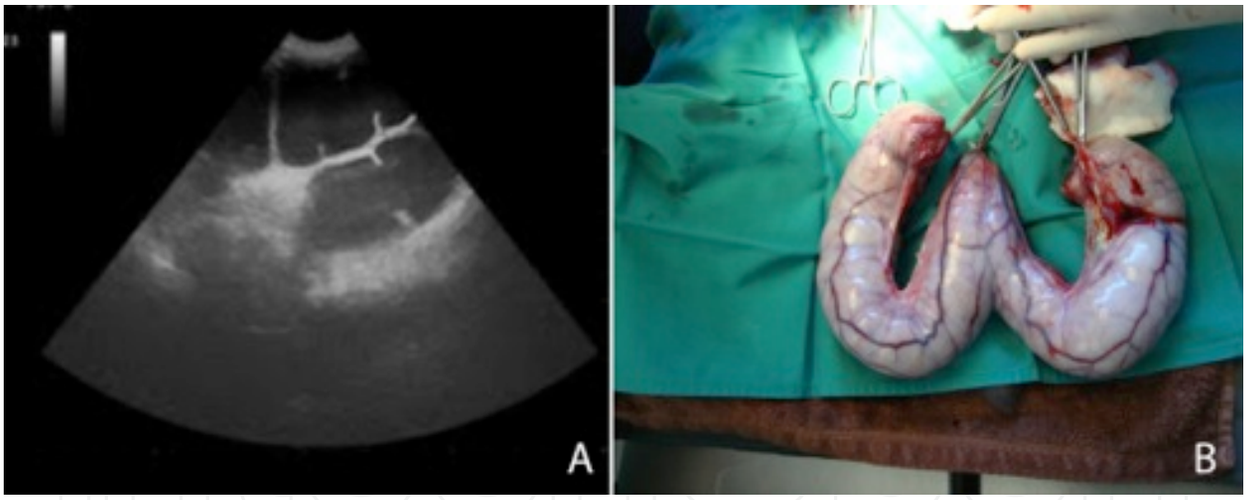

Figure 3. Pyometra in a female cat. (A) Abdominal ultrasound of a queen with pyometra showing a marked uterine distention with a narrow uterine wall, and the presence of hypoechoic intraluminal fluid; the loss of definition of the uterine contour and the unfolding of uterine walls are also observed. (B) Macroscopic aspect of the uterus after surgical excision.

5. Treatment

Pyometra is considered an emergency; thus, treatment should be rapid and aggressive due to the risk of septicemia, endotoxemia, azotemia, uterine rupture, peritonitis and shock [9, 10, 24,

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34]. Surgical treatment (ovariohysterectomy—Figures 3B and 4) associated with supportive therapy is considered the treatment of choice [25, 26]. Support treatment includes intravenous fluid therapy and antibiotics administration [19]. Fluid therapy is directed to correct fluid deficits and electrolytic and acid-base imbalances, to correct azotemia and to maintain adequate tissue perfusion [6]. Whenever possible, antibiotics should be chosen based on bacterial culture and sensitivity. However, these procedures may take longer than the time available to recover the female from a life-threatening situation. Therefore, if not possible or during pending culture results, wide broad bactericide antibiotics effective against the most common bacteria are recommended, including ampicillin, amoxicillin + clavunalate, trimethoprim sulfonamide, cephalosporins and enrofloxacin [6]. Ovariohysterectomy rapidly and permanently eliminates the site of infection, and most cats recover successfully [19].

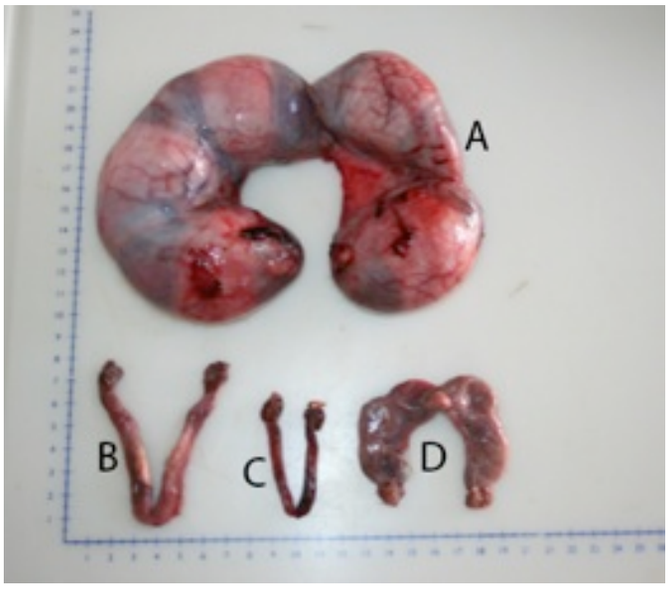

Figure 4. Different morphological aspects and sizes of queen's uterus collected at ovariohysterectomy. Each specimen represents a different clinical condition: (A) late-pregnant uterus; (B) uterus in a follicular stage; (C) uterus in anestrous; (D) uterus with pyometra.

Medical treatment could be considered in queens with reproductive added value, which are clinically stable and present an open-cervix pyometra [24, 35]. Medical treatment is directed to avoid synthesis or effects of progesterone, and to evacuate the uterine content.

Treatment with prostaglandins (natural or synthetic prostaglandin F2α, such as cloprostenol) or with aglepristone (an anti-progestagen) has proved to be effective in feline pyometra [36–39]. However, care should be taken before starting a treatment with prostaglandins as they should not be used in closed-cervix pyometra due to the risk of uterine rupture [24, 35, 38]. Prostaglandins promote luteolysis, consequently decreasing plasma concentrations of progesterone, and stimulate myometrial contraction leading to uterine evacuation [24, 40]. Mild and transient side effects, such as vocalization, panting, restlessness, grooming, tenesmus, salivation, diarrhea, mydriasis, emesis, urination and lordosis, can develop after prostaglandin administration [38, 39].

Aglepristone binds to the progesterone receptors and consequently inhibits progesterone effects. Once progesterone influences are withdrawn, the cervix will open and allow the elimination of the uterine content [37]. No side effects were observed in cats treated with aglepristone [37]. This compound may be used to treat a closed pyometra if the animal is stabilized and the risks of septicemia are residual. Prostaglandins and aglepristone can be used in association [25]. One good approach is to start the treatment with aglepristone and to associate the prostaglandins 24 to 48 h after the first aglepristone administration [37].

Queens submitted to medical treatment will be at risk for recurrence of pyometra at every ovulation after treatment if they do not become pregnant. To prevent it, they should be bred on the next cycle and then spayed when no longer needed for breeding [34].

6. Morphological aspects of cystic endometrial hyperplasia

It is well acknowledged that CEH pathogenesis involves the hyperplasia of the endometrium with cyst formation, which causes the accumulation of endometrial secretions [8], first into the glands lumen and then into the uterine lumen, with variable amount of serous, mucous, or purulent (neutrophils) content [6, 26].

Cysts develop from the endometrial glands (Figure 5A), and their number, size, distribution, histological morphology, and clinical relevance are variable [8]. As previously stated, CEH is usually a silent pathology, mainly if the cysts are small-sized. Cystic endometrial hyperplasia can progress into pyometra, and may or may not be associated with bacterial infection [41].

The morphology of CEH is variable, ranging from small gland dilatations to cystic structures occupying the entire endometrium and protruding into the uterine lumen. It is possible that the increased pressure of the cystic fluid modifies the morphology of glandular epithelium from cubic to squamous. In our experience (unpublished data), the size and number of cysts are not related with the grade of endometritis (mainly composed of a plasma cell and macrophages infiltrate) or with pyometra.

Dow [26] classified the severity of the CEH in four grades, being grade 1 the less severe, characterized by an endometrium with approximately normal dimensions and the presence of small cysts; and grade 4, the most severe, characterized by a significantly thickened endometrium or an atrophic endometrium with large ulcers associated to pyometra [26]. Different degrees of inflammation exist, ranging from a discreet mononuclear endometrium infiltration around the cysts in grade 2 to a severe infiltration of neutrophils, macrophages, and plasma cells in grade 4 [8].

The stimulus for connective tissue deposition around small aggregates of endometrial cystic glands can cause expansion and protrusion of a small portion of the endometrium, originating endometrial polyps, which are considered as morphologic variations of CEH. Queens can present single or multiple endometrial polyps, with variable dimensions [8], which can be spread along the uterine horns due to estrogen or progesterone influence [7].

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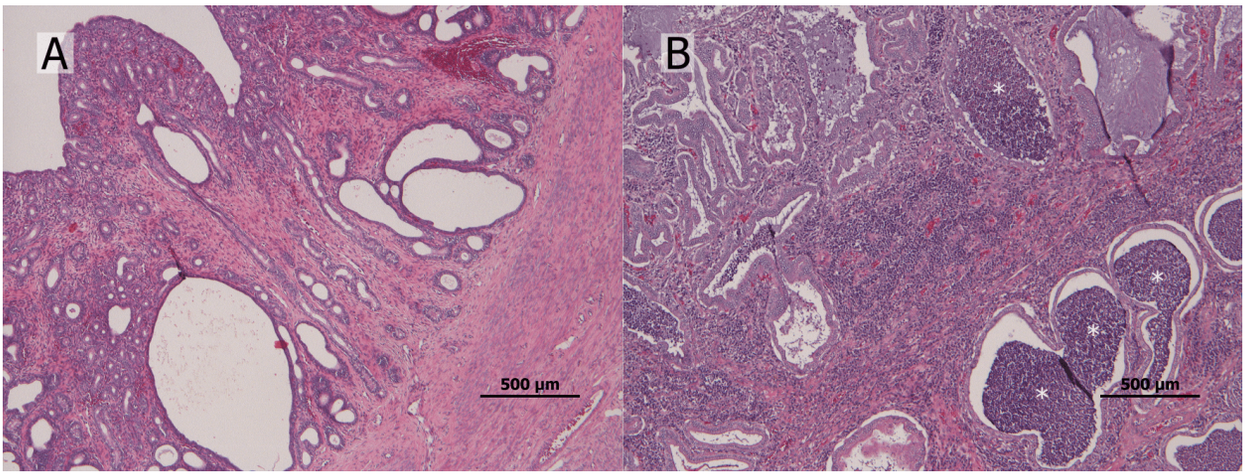

Figure 5. (A) Histological aspect of grade 2 CEH showing a hyperplastic endometrium with differently sized cysts. (B) Histological aspect of pyometra in a queen. Note the endometrium with cystic structures filled with neutrophils (*) opening into the lumen (arrow). An intense mononuclear infiltrate in endometrium characterizes endometritis (arrowhead) in a hyperplastic endometrium when concomitant CEH exists. Hematoxylin and Eosin. Bar = 500 µm.

7. Morphological aspects of pyometra

Morphological aspects of pyometra in queens are similar to those observed in the bitch and other species. The enlargement of the uterus is variable, ranging from a subtle increase to a severe enlargement in the endometrium dimension when associated to harsh glands and epithelium hyperplasia. The major feature of pyometra is the presence of neutrophils in the lumen of the uterus [7]. The glands are filled with mucous and neutrophils (Figure 5B) in a hyperplastic endometrium, evolving to the rupture of cysts into the lumen. Contrasting to that observed in the healthy endometrium, a raise of macrophages and B lymphocytes in the lumen and in the endometrium is observed following an initial rise in neutrophils, but only minor changes on the values for T lymphocytes are reported [23]. An asymptomatic pyometra often evolves to an atrophic and ulcerated endometrium, the final phase of this disease. The myometrium becomes thinner and uterine rupture can be eminent in more severe cases.

Endometritis is a concomitant feature with pyometra (Figure 5B). In the beginning of the process, neutrophils are the predominant cell type in the endometrium stroma, but macrophages and mainly plasma cells become more intense in chronic cases, presenting ulcerated and atrophic endometrium [7].

8. Feline endometrial adenocarcinoma: frequency, morphological and clinical aspects

Adenocarcinoma of the uterus is a malignant neoplasm, which arises from the endometrial epithelia [42]. Although reported in the rabbit, cow, rat, mouse, guinea pig, horse, dog, and

cat [43], it is considered to be rare in domestic animals [44, 45]. In the literature, feline endometrial adenocarcinoma (FEA) is referred as an infrequent tumor [44]. However, recent reports of FEA suggest that the disease might be more common than assumed, and its incidence may be underestimated [18, 47, 46]. Feline endometrial adenocarcinoma is usually reported in geriatric queens, older than nine years of age [42, 48–50], but recently Cho et al. [51] and Payan at al. [18] reported FEA in young queens, less than two and one years old, respectively [18, 51].

The common practice of elective ovariohysterectomy in cats is being referred as protective from uterine neoplasia [11, 52]. Notwithstanding, the rarity of these tumors might be related to inadequate post-surgical or post-mortem evaluation of the genital tract [7, 53]. In fact, most clinicians do not require a histopathological evaluation of genital apparatus based on the assumption that "it is normal" or "only a pyometra".

Data related to the factors involved in the development of feline endometrial adenocarcinomas (FEA) are still insufficient. However, it seems probable that the endogenous or exogenous ovarian steroid hormones, associated to pyometra development, might also influence endometrial carcinogenesis and tumor progression [1, 18]. As recently reported, according to the database of our laboratory in a 13-year period, feline endometrial adenocarcinoma was diagnosed in 20.30% of cases ($n = 37/197$) while 33.5% (66/197) presented uterine inflammatory disease [12]. However, in 41.16% (81/197), the queen failed to manifest signs of uterine dysfunction or history of infertility. FEA either evolves as a silent disease [3, 47] or is associated to nonspecific and vague clinical signs that can be associated to other uterine disorders, including CEH, pyometra, or abortion. Therefore, there is a strong possibility that these tumors may be underdiagnosed [16, 18, 47].

Uterine tumors are more commonly found in sexually intact queens [54], but there are three reported cases of FEA in the uterine stump of ovariohysterectomized cats [44, 43, 54]. As such, these cases represent unusual complications following an incomplete ovariohysterectomy of the uterine body in a previously undiagnosed diseased uterus [44, 54].

Saraiva et al. [47] described three different histotypes of FEA based on cell features, growth pattern, and invasiveness, which included papillary serous carcinoma, clear cell carcinoma and "in situ" (non-invasive) carcinoma [16]. Microscopically, this classification resembles the human endometrial carcinoma classification [55]. Macroscopically, these patterns are indistinguishable, presenting as a multiple whitish papillary masses or a diffuse thickening of the endometrium along both uterine horns and corpus, which are better appreciable in a longitudinal section of this organ. Occasionally, the uterine wall may be thinner (atrophic) and when a concomitant pyometra is present, a purulent exudate may be observed in the lumen. Tumor invasion of the myometrium may be detected, and serosa rupture can occur promoting peritonitis and peritoneal carcinomatosis. Distant metastases in lungs or liver were seldom reported [54].

Regarding the cyclic uterus, in the presence of tumors we found higher numbers of macrophages and T lymphocytes. An increased number of B cells was only observed in pyometra cases and in FEA cases associated with pyometra. These findings suggest that B lymphocytes may be more relevant in uterine inflammation and that T cells may be more important in

endometrial tumor oncobiology. These findings deserve more investigation to ascertain the real function of the various cell types on the etiopathogeny of uterine inflammation and neoplasia [23].

9. Hidden behind feline pyometra

In our experience, pyometra may not be the only uterine pathology observed in a queen that presents a mucous, hemorrhagic, or purulent vulvar discharge accompanied with other clinical signs compatible with pyometra.

Chronic inflammation associated with pyometra has been suggested to have a tumorigenic effect, and the inflammatory process may itself mask an underlying neoplasm in an under-evaluated uterus [56]. Association of pyometra with FEA was also suggested by some authors reporting cases of endometrial carcinoma in queens with pyometra [1, 16–18, 44]. Data related to the etiological factors involved in the development of feline endometrial adenocarcinomas are still scarce; however, it seems possible that the endogenous or exogenous ovarian steroids hormones associated with pyometra development might also influence endometrial carcinogenesis and tumor progression [1, 18].

Our laboratory records show that approximately 44% (29/66) of diagnosed pyometra co-existed with FEA, and that 24.2%(16/66) had concurrent CEH.

The clinical anamnesis is an important tool that must be explored to exclude the possibility of gestation or abortion. Whenever ovariohysterectomy is the adopted solution, the uterus must be totally excised, including the body and the cervix in the excised specimen. The histopathology is the unique complementary analysis that can distinguish and discard pyometra from other uterine lesions. Thus, it is of utmost importance to submit these organs to histopathological examination. At surgery, if any part of the uterine horns or the uterus is left in place (partial hysterectomy), it can bring problems in a near future, as some description of FEA [25] and pyometra were reported in uterine stumps of spayed queens [5, 14, 47, 54]. So, the complete and careful surgery associated with histopathological observation, alongside to a correct clinical monitoring, are the most important points to discard possible lesions that could be hidden behind a pyometra.

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